Hyperammonemic Coma Presenting as Hashimoto’s Encephalopathy

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Abstract
Hyperammonemia is commonly encountered in active liver disease. Evaluation of patients having hyperammonemia with normal liver function is difficult. We present a case referred to us as undiagnosed hyperammonemic coma with normal liver function, who was subsequently diagnosed to have Hashimoto’s encephalopathy. In patients with hyperammonemia without hepatic dysfunction, one must search for the presence of hypothyroidism. Hashimoto’s encephalopathy though described to be rare in literature, is often underlooked. In patients with undiagnosed coma, one must look for it as it is easy to diagnose and treat.

INTRODUCTION

The normal blood ammonia levels range from 10 to 40 mmol/L. Hyperammonemia is defined as serum ammonia levels of more than 40 mmol/L. It is commonly encountered in presence of active liver disease. We hereby present a case referred to us as undiagnosed hyperammonemic coma wherein the liver function was normal and subsequently was diagnosed to have Hashimoto’s encephalopathy with possibility of underlying chronic inactive autoimmune hepatitis. In the patients presenting with hyperammonemia and having a normal liver function, the following causes must be considered; urinary tract infection with urease producing organisms, urea cycle enzyme deficiencies, distal renal tubular acidosis, urinary diversion, long term valproate therapy and hypothyroidism. There is limited literature on mechanism of hyperammonemia in hypothyroidism simulating liver failure. In patients with evidence of hyperammonemia and absence of evidence of hepatic dysfunction, one must search for the presence of hypothyroidism.

CASE

A 48 years old female was referred to us as a case of undiagnosed hyperammonemic coma. She was asymptomatic six months back when she developed menorrhagia and was diagnosed to have dysfunctional uterine bleeding. She was seen by a gynecologist and diagnosed to have fibroid uterus. Hysterectomy was done under general anesthesia. She was having no medical complications preoperatively as assessed by the general physician. She had an uneventful operative course and was discharged in a healthy state. Two days later, she started showing signs of confusion and started becoming socially withdrawn. Over a period of one week she became practically mute. She was referred to a Neurophysician/ Psychiatrist for her symptoms. She was evaluated with routine blood investigations, s. electrolytes, hepatic function tests, renal function tests, brain imaging and electroencphelography (EEG). Except for s.ammonia level of 133 microgram/dl and S. tSH of 9.29 MI u/L, rest of the investigations were within normal limits. Her MRI brain showed no abnormality. Her EEG showed mild diffuse background slowing. Her sonography of abdomen showed hepatomegaly but liver echo-texture was normal. She was managed on the usual lines of hepatic cause of hyperammonemia by restriction of protein and lactulose. She was started on low dose of Levothyroxine (50 microgm). However she had a steady deterioration in her symptoms. There was progressive cognitive decline and mutism with development of bilateral upper limb tremors and rigidity. She was referred to us for further evaluation. Her vitals were normal. On central nervous system examination, she was found to have a mute state with bilateral upper limb tremors and rigidity.

Two days later during the hospitalization, she developed an episode of generalized tonic clonic convulsion and developed delirium. Her general examination was normal. On per abdomen examination, there was mild hepatomegaly. She was reinvestigated with the routine blood tests, thyroid function tests, renal and liver profile, HIV, HB5Ag, anti HCV, s. electrolytes. Her CSF was done for routine examination, oligoclonal bands, cytology, cryptococcal antigen, toxoplasma, CMV, HSV and Lyme. The CSF examination showed a protein of 114mgs%, normal sugar and 01 cell which was a lymphocyte. Rest
of the investigations in CSF were normal. Her urine was screened for amino acids and particularly for orotic acid and porphyrins, which was negative. Hypercoagulable panel, occult malignancy work up and toxicology screen were done, all the tests were negative. Work up for Wilson’s disease was negative. An MRA brain with MRV was repeated which was normal. A repeat EEG was done which showed diffuse slowing. A liver isotope scan was done which showed moderate hepatomegaly with early chronic liver disease. There was no evidence of portal hypertension. A repeat thyroid profile showed normal levels of free T3 and T4 and elevated s. tSH. (10.2 MIU/ML). Thyroid antibodies were sent. Her thyroglobulin antibody level was found to be positive with a titer of 1000IU/ML(normal level being less than 100 IU/ML). Her thyroperoxidase antibody (TPO) level was found to be 430 IU/ML (normal level being less than 50 IU/ML) Her thyroid scan was done which showed mild thyromegaly with diffuse uptake of the tracer. Considering the early chronic liver disease found on liver scanning and negative viral markers of hepatitis, a liver biopsy and antibodies for autoimmune work up like anti SMA (smooth muscle antibody), anti LKM (liver and kidney mircosome), antinuclear antibodies were planned but was withheld as the patient’s relatives denied the same.

However, a hypothesis of underlying chronic inactive autoimmune hepatitis based on imaging was made. Considering the elevated proteins in CSF with no pleocytosis and elevated titers of antithyroid antibodies, she was started on full dose of injectable steroid (methyl prednisolone-1gm/day). On the next day, she started showing signs of improvement with regaining of normal consciousness and there was abatement of tremors/rigidity. She fulfilled the criteria required for the diagnosis of Hashimoto’s encephalopathy. She was offered a complete course of intravenous steroid for seven days and subsequently put on oral steroids.

With the treatment of hypothyroidism and steroids, her ammonia levels started to fall and normalized over three days. The long term plan is to keep her on maintenance dose of steroid and plan a gradual taper. She is in regular follow up and doing well with steroids. Moreover a repeat anti TG and anti TPO antibody profile at one month of treatment is showing reduction in the titers of the antibodies with anti TG being 200 IU/ML and anti TPO being 150 IU/ML.

**DISCUSSION**

Hashimoto’s encephalopathy has been described as an encephalopathy with acute or sub acute onset, accompanied by seizures, tremors, myoclonus, ataxia, stroke like episodes. It has a relapsing/remitting course or a progressive one. It was first described in 1966 by Brain et al. Searching the Medline database from August 1966 to December 2007 for Hashimoto’s encephalopathy, a total of 114 citations were found. However we could find only one citation with a mention of hyperammonemia in Hashimoto’s encephalopathy. Hyperammononemic coma is known to occur in Myxedema.²

The effect of thyroxin metabolism on ammonia is not well understood. Although protein synthesis is reduced in patients having hypothyroidism, urea production and activities of urea cycle is shown to be increased in the animal models. It is postulated that an increased load of nitrogen products in hypothyroidism increases the production of ammonia. However the exact role of hypothyroidism in hyperammonemic coma as a direct inciting factor or a precipitating factor in patients with underlying chronic liver disease is not accurately known.³ ⁵

The literature has shown that there is a complex interaction between liver and thyroid. Hyperammonemia accompanies profound hypothyroidism in patients with coexisting liver disease and hence in patients showing no improvement with routine line of management and those having an existing liver disease, a search for hypothyroidism is justified. Hypothyroidism is known to exacerbate hyperammonemia and porto systemic encephalopathy in patients having well compensated liver disease too.⁶

Autoantibodies to thyroglobulin (TG) are often present in patient’s with autoimmune thyroid disease. Approximately ten percent of healthy individuals have presence of anti TG antibodies at low level while higher levels are found in 30 and 85 % of patients with Grave’s disease and Hashimoto’s thyroiditis respectively. Elevated levels of anti TPO however is specific for the presence of thyroid disorder and is not found in healthy individuals having anti TG antibody positivity. Moreover the demonstration of falling titers of the same with the treatment favours the association of the antibodies to the disease.⁷ ⁸

Our patient can be postulated to have mild underlying liver dysfunction, and that the persistent hyperammonemia not responding to the regular line of treatment was attributed to the presence of underlying hypothyroidism. The chronic hepatitis associated with autoimmune hepatitis has been shown to range from subclinical illness without symptoms, with only abnormal liver chemistries to a disabling liver disease.⁹

A review of the literature reported improvement in 98% of cases of Hashimoto’s encephalopathy treated with steroids, 92% treated with steroids and Levothyroxine, and 67% treated with Levothyroxine, while 9% of cases did not improve with any of the above combinations. 90% of cases stayed in remission even after discontinuation of treatment. Duration of disease has been reported to range between 2 and 25 years. Cases of the relapsing/remitting type usually did better than the progressive type, a few of which developed irreversible persistent cognitive impairment.¹⁰

**CONCLUSION**

Presentation of Hashimoto’s encephalopathy with hyperammonemia coma with well compensated liver disease is quite rare. In every patient of hyperammonemia, not responding the usual line of treatment, a search for hypothyroidism is justified. A high index of suspicion for
Hashimoto's encephalopathy is required as it is a treatable cause and can be easily diagnosed with antithyroid antibody levels.

REFERENCES